REMARKS

Claims 1, 6, 7, 12-16, 28, 29, 31 and 32 are pending. Through this Amendment, claim 1 has been amended, claim 32 has been added, and claim 26 has been cancelled.

Applicants' Response to 35 U.S.C. §102 Rejection over Short

Claims 1, 6, 7, 12-16, 26, 28 and 31 were rejected under 35 U.S.C. §102(e) as being allegedly anticipated by WO 2004/040308 A1 to Short et al. (hereinafter "Short") as evidenced by Dako General ELISA Procedure, February 2002 (hereinafter "Dako").

Applicants have amended claim 1. In particular, claim 1 has been amended to incorporate the specific steps of incubation with PBS, washing and incubation with TSG-6. Support for amendments can be found through out the specification. Specifically, support for the incubation step with PBS can be found on page 15, line 20. Support for the washing step can be found on page 15, line 21-23. Support for the step including tumor necrosis factor-inducible gene 6 protein can be found on page 14, lines 14-15 and page 15, lines 24-26. It is noted that the specification refers to "TSG-6" and not specifically "tumor necrosis factor-inducible gene 6 protein". One of skilled in the art would clearly appreciate that TSG-6 is a tumor necrosis factor-inducible gene 6 protein. Accordingly, inclusion of this term does not include new matter. Further, one of skill in the art would appreciate that the plates are incubated with a solution comprising TSG-6 and thus the amendments are fully supported by the specification. Amended claim 1 provides a method for selective disassociation of at least one glycosaminoglycan which is bound by a specific technique.

The present specification provides a method for selective removal of molecules that are bound to a plasma polymerized surface and for the selective removal of molecules that are bound to proteins, nucleic acids or carbohydrates, which are bound to a plasma polymerized surface. (See Instant Specification, page 3, lines 30-31, page 4, lines 1-10 and page 11, lines 20-30.) As a result of this method, as can be seen from the figures and the examples, plasma polymerized plates that were treated with PBS and coated with heparin provided greater absorbance than

plates that did not have PBS or plasma polymerization. Further, as shown in Figure 5 and described in Example 5 on page 19, the binding of heparin on an allylamine surface is salt-strength dependent based on the ionic interaction. Accordingly, the amount of *bound* glycosaminoglycan can be reduced by contacting the *bound* glycosaminoglycans with an agent that includes a salt concentration level between 0.5 M and 2.0 M. The strength of the concentration affects the level of disassociation. In this manner, the extent of disassociation can be controlled.

In the Examiner's "Response to Arguments" section of the Office Action, the Examiner acknowledged that Short does not "expressly teach the selective disassociation of bound heparin from a plasma polymerized surface." (Office Action, at page 21). However, the Examiner alleged that Short "carries out the process during normal operation", particularly with using an ELISA technique. (Office Action, at page 21).

As is known in the art, enzyme-linked immunosorbent assay (ELISA) is used for detecting the presence of *bound* biological agents. Utilizing ELISA with a low concentration of NaCl washing solution merely removes unbound biological material, but does not remove *bound* biological material. Removing unbound biological material is entirely different from the method set forth in the instant claims wherein glycosaminoglycan is bound by a specific process and then *selectively* disassociated. Accordingly, Applicants respectfully submit that utilizing washing buffers for ELISA, which removes <u>*unbound*</u> biological materials, and the method according to the present claims is easily distinguishable to one of skill in the art.

As is known in the art, immobilization or binding of a biological material typically involves passive adsorption onto a plasma polymerized surface. Once a biological material, such as a glycoaminoglycan, is bound to a plasma polymerized surface it cannot be simply desorbed by washing or any typical assay, such a ELISA. (See Instant Specification, page 10, lines 13-20).

As set forth in the present claims, the present invention is directed to the selective removal or disassociation of bound glycosaminoglycan from a plasma polymerized surface. Nowhere in the cited references is this method disclosed or suggested. It is respectfully submitted that claims 1, 6, 7, 12-16, 28, 31 and 32 are patentable over Short.

Applicants' Response to 35 U.S.C. §103 Rejection over Short & Whittle, Schwartz, Marchant and Schwarz

Claims 1, 6, 7, 12-16, 26, 28 and 31 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over WO 01/031339 to Short & Whittle (hereinafter "Short & Whittle"), as evidenced by WO 98/19161 to Schwartz (hereinafter "Schwartz"), in view of WO 94/10938 to Marchant (hereinafter "Marchant") and Schwarz et al., Glycobiology, 2003, vol 13, No. 11, p. 749-754 (hereinafter "Schwarz").

The Examiner continues to reiterate that the "surface taught by Short & Whittle is identical to the surface used in the claimed method". (Office Action, pages 21-22) The Examiner acknowledged that Short & Whittle does not teach a salt concentration of about 500mM to 2 M NaCl or the selective disassociation of a biological molecule, but alleged that this would be obvious based on the teachings of Marchant and Schwarz. Applicants disagree.

As discussed above, claim 1 has been amended to include the specific steps of incubation with PBS, washing, incubation with TSG-6 and contacting with an agent having a salt concentration of between 500 mM NaCl to 2 M NaCl. This process is not disclosed or suggested in Short & Whittle. Also, there is no rationale in Short & Whittle for altering the salt concentration to selectively disassociate bound biological molecules.

Marchant is directed to a plasma polymer-modified surface that may have heparin attached thereto. Contrary to the Examiner's allegation, Marchant does not teach "selective separation of carbohydrates". Marchant merely discloses how to prepare high-affinity heparin

by utilizing an affinity column. (See Marchant, pages 13-15). Marchant does not disclose binding heparin to a surface and then selectively disassociating the heparin with a salt gradient.

The Examiner relied on Marchant to support the allegation that it would be obvious to use salt concentrations in the amounts claimed by Applicant. Applicants respectfully submit that the Examiner's interpretation of this reference is misplaced. Marchant does not disclose the use of an agent as set forth in claim 1 for disassociating a bound biological entity. As mentioned above, in Marchant the HA-heparin is made from utilizing a solution of crude heparin that is subjected to an affinity column. Any heparin that is not adsorbed to the surface of the column is eluted. This eluted heparin was never bound – as it was never adsorbed. Accordingly, Marchant adds nothing of relevance to Short & Whittle. Furthermore, nowhere in Marchant is it disclosed or suggested that the bound HA-heparin is then removed from a plasma polymerized surface via selective disassociation. Accordingly, one of skill in the art would not interpret Marchant to read on the present claims or render the present claims obvious.

Applicants also traverse the inclusion of the Schwarz reference. Schwarz teaches a carbohydrate array to be used for profiling antibodies. The substrates of Schwarz are not plasma polymerized. Accordingly, it is unclear why one of skill in the art would combine a plasma polymerized plate with the carbohydrate array of Schwarz and expect any expectation of success. Furthermore, Schwarz teaches away from dissociation considering its statement that binding is detected after washing the glycan array with a 2M solution. (Schwarz, page 753).

The Examiner alleged that one of skill in the art would be motivated to alter the salt concentration through routine experimentation. The Examiner alleged that one of skill in the art would be motivated to do so because it would be desirable to re-use the surfaces. Furthermore, the Examiner alleged that utilizing the buffers would provide a reasonable expectation of success based on the teachings of Marchant. Applicants traverse. Nowhere in any of the references provided by the Examiner is it disclosed or suggested to re-use the surfaces. Accordingly, it is unclear how such one of skill in the art would be motivated to do so based on these teachings.

It is respectfully submitted that claims 1, 6, 7, 12-16, 28, 29, 31 and 32 are patentable over Short & Whittle, Schwartz, Marchant and Schwarz, each taken alone or in combination.

Applicants' Response to 35 U.S.C. §103 Rejection over Short & Whittle, Schwartz, Hutchens and Marchant

Claims 1, 6, 7, 12-16, 26, 28, 29 and 31 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Short & Whittle, as evidenced by Schwartz, in view of WO 98/59360 to Hutchens (hereinafter "Hutchens") and Marchant.

The Examiner acknowledged that Short & Whittle does not teach a carbohydrate and that the combination of Short & Whittle with Hutchens does not teach the salt concentration of 500 mM to 2 M NaCl. The Examiner alleged that:

> One of ordinary skill in the art, at the time the invention was made, would have been motivated to use a salt concentration of about 500 mM NaCl to about 2 M NaCl for the selective disassociation of a glucosaminoglycan because it would be desirable, to reuse the plasma polymerized surface…for investigation of ionic strength of carbohydrate-protein interactions, as taught by Hutchens.
>
> One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because NaCl is routinely used in the standard ionic strength based salt eluants, as taught by Hutchens. In addition, as taught by Marchant, use of the 3 M NaCl linear salt gradient elution of increasing ionic strength provides selective separation of carbohydrates, such as heparin polysaccharides.
>
> (Office Action, at page 11).

As stated above, Marchant does not teach utilizing a specific salt concentration to selectively disassociate bound heparin from a plasma polymerized surface. In contrast, Marchant merely describes how to prepare HA-heparin and how HA-heparin has better anticoagulant activity than crude heparin.

The Examiner also relied upon Hutchens to arrive at the allegation that the claims are obvious. Hutchens is directed to retentate chromatography. In retentate chromatography, "analytes which are retained on the adsorbent are detected." (Hutchens, page 4, lines 20-21). This is in contrast with conventional chromatography in which "analytes are eluted off of the adsorbent prior to detection." (Hutchens, page 4, lines 21-22). It is unclear how retantate chromatography is relevant to plasma polymerization or selective disassociation. The Examiner points to Hutchens' disclosure of washing the adsorbent with eluants and different concentration levels of eluants. Similar to the discussion of Marchant above, one of skill in the art would appreciate that the eluants of Hutchens are simply removing unbound biological material. One of skill in the art would also appreciate that these materials were not bound to a plasma polymerized surface. Therefore, Hutchens adds nothing of relevance to Short & Whittle, Schwartz or Marchant.

Again the Examiner alleged that one of skill in the art would be motivated to alter the salt concentration through routine experimentation and that doing so because would be desirable because of the ability to re-use the surfaces. Applicants again traverse. Nowhere in any of the references provided by the Examiner is it disclosed or suggested to re-use the surfaces. Accordingly, it is unclear how one of skill in the art would be motivated to do so based on these teachings.

It is respectfully submitted that claims 1, 6, 7, 12-16, 28, 29, 31 and 32 are patentable over Short & Whittle, Schwartz, Hutchens and Marchant, each taken alone or in combination.

Applicants' Response to Double Patenting Rejection

Claims 1, 6, 7, 12-16, 26, 28, 29 and 31 were rejected on the grounds of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 3-25 and 33-38 of co-pending U.S. Application No. 10/533,063, in view of Schwarz and Hutchens.

Claims 1, 6, 7, 12-16, 26, 28, 29 and 31 were rejected on the grounds of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 85, 87, 90-94, 96, 102, 103, 108, 109 and 112-123 of co-pending U.S. Application No. 10/560,210, in view of Schwarz and Hutchens.

Claims 1, 6, 7, 12-16, 26, 28, 29 and 31 were rejected on the grounds of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 41, 47-50 and 54 of co-pending U.S. Application No. 10/509,431, in view of Marchant, Schwarz and Hutchens.

Applicants respectfully submit that the amendments herewith overcome the double patenting rejection. However, in the interest of advancing prosecution, Applicants will consider filing a terminal disclaimer, or canceling/amending claims, as necessary once any of the claims have been allowed. Applicants request the issuance of an *Ex parte Quayle* action if this case is in all other respects found allowable.

Favorable action is earnestly solicited. If there are any questions or if additional information is required, the Examiner is respectfully requested to contact Applicants' attorney at the number listed below.

Respectfully submitted,

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